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Efficacy of photodynamic therapy in women with HSIL, LSIL and early stage squamous cervical cancer: a systematic review and meta-analysis

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ABSTRACT

Background: We sought to conduct a systematic review and meta-analysis of randomized and non-randomized clinical trials to assess the efficacy of photodynamic therapy (PDT) in cervical epithelial neoplasia (CIN) and early-stage cervical cancer. Additionally, according to the results, we tried to consider which stage of CIN is more sensitive to PDT.

Methods: A systematic search was conducted using electronic databases including PubMed, ClinicalTrials.gov, the Cochrane Library, and Google Scholar. Inclusion criteria: all patients had confirmed low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or an early-stage cervical cancer – the cancer is less than 3 mm deep into the cervix -IA; type of photosensitizer and any type of wavelength. Exclusion criteria: women who were previously treated with PDT; Risk of bias assessment was carried out for each study included in the systematic review using the Cochrane Handbook for Systematic Reviews of Interventions: RoB-2 was used to assess the risk of bias in randomized studies, while ROBINS-I – in non-randomized ones.

Results: We identified 2213 publications, but only 6 met the inclusion criteria and were included in the synthesis. PDT is most effective when patients have CIN 2 or photosensitizer is administered intravenously.

Conclusion: Based on our systematic review and meta-analysis, it could be concluded that photodynamic therapy may be a practical approach in CIN (LSIL) regression compared with placebo. Nevertheless, we need more evidence and long-term follow-up to answer all questions thoroughly.

1. Introduction

Cervical cancer remains one of the most diagnosed cancers among women after breast cancer. Regardless of numerous advances made in diagnosing and treating this cancer, recent data shows that cervical cancer incidence and mortality are higher in low-resource/developing countries (mostly African and Latin American) with poor diagnostic and treatment opportunities. [1,2]

Cervical squamous intraepithelial lesion (also known as cervical intraepithelial neoplasia) is a pre-malignant state, i.e., dysplastic changes of the uterine cervix that, if left untreated and uncontrolled, can progress to cervical cancer. Classification of CINs is based on a morphological picture and includes CIN I (or low-grade squamous epithelial lesion – LSIL), CIN II, and CIN III (also referred to as CIN2+ or high-grade squamous epithelial lesions – HSIL).

Initially, the diagnosis of CIN was implemented into clinical practice to select patients who have increased risk (almost 20-fold in case of HSIL) of developing cervical cancer and slow down its progression using various therapeutic methods. According to current recommendations, treatment options for CIN include both invasive and non-invasive procedures, such as laser surgery, diathermocoagulation, cryotherapy, large loop excision of the transformation zone (LEEP/LLETZ), cold knife conization (CKC), as well as such standard methods as radio- and chemotherapy. [3] Despite their positive effect on CIN regression, several severe side effects apprehensions regarding their routine usage. Thus, the global medical community should keep searching for alternative methods of treatment.

Photodynamic therapy (PDT) is a modern and non-invasive

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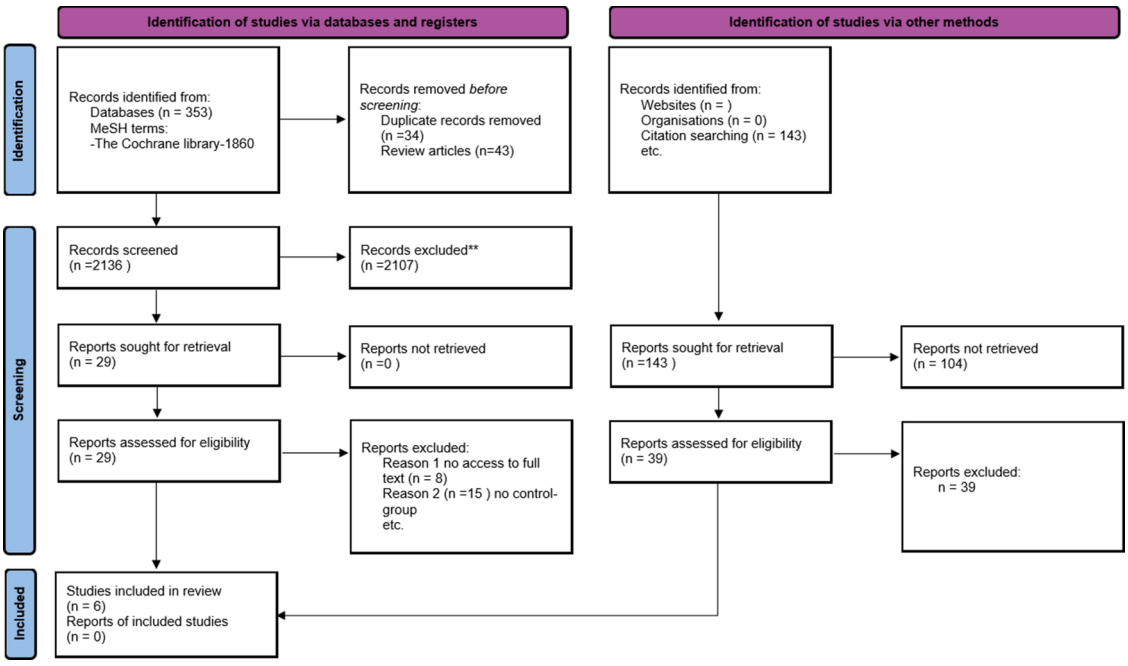

Fig. 1. Flow-diagram of the search strategy.

procedure used to treat non-neoplastic and neoplastic diseases. It is based on the topical or systemic application of photosensitive molecules, called photosensitizers (such as 5-aminolevulinic Acid and other porphyrins), that selectively accumulate in abnormal tissues and cause cellular oxidative stress via generation of reactive oxygen species after exposure to light of a specific wavelength. It is successfully used in many fields of medicine and has promised itself in treating CINs and cervical cancer. [4]

Therefore, our study aims to evaluate whether PDT is an effective treatment for women with LSIL and HSIL and early-stage cervical cancer.

2. Materials and methods

This study has been registered in the PROSPERO international prospective register of systematic reviews by the National Institute for Health Research (NIHR). Protocol and registration number: PROSPERO 2021 CRD42021229141.

The present systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for reporting systematic reviews [5]. Our review included all published research articles that evaluate the efficacy of photodynamic therapy in women with LSIL, HSIL, and early-stage squamous cervical cancer. Studies considered were randomized clinical trials (RCT) and non-randomized clinical trials (prospective cohort, retrospective studies). Studies only in English were accepted.

A systematic search was conducted in electronic databases including PubMed, ClinicalTrials.gov, the Cochrane Library, and Google Scholar. The restriction on the date of publication is 2021 years and later.

Three reviewers (K. M., J. D., A. Kh.) independently screened titles and abstracts of the identified studies and then read the full texts of preselected articles. Disagreement between the reviewers was resolved through a discussion with a fourth reviewer (R. M.). The authors of the original articles were contacted if necessary.

The search strategy in the electronic database Pubmed was the following. Firstly, using the advanced search builder on PUBMED, the following combination of the search terms was conducted: (photodynamic treatment OR PDT) AND (cervical cancer OR CIN OR LSIL OR HSIL), no filters and limits were used. Additionally, the search was conducted, using MeSH-terms on PubMed ("Photochemotherapy"[Mesh]) AND (("Uterine Cervical Neoplasms"[Mesh]) OR ("Cervical Intraepithelial Neoplasia"[Mesh]) OR ("Squamous Intraepithelial Lesions"[Mesh])). Secondly, all found articles were researched by the title and the abstract. After that, the full texts of articles that were considered relevant were analyzed. Finally, the reference lists of the selected articles were searched for additional potential studies. The last date when the electronic database PUBMED was searched is 26.02.2021.

In addition to PUBMED, the search strategy of the electronic database Cochrane library will be represented. First, the search on Cochrane was conducted using the advanced search and the following keywords: cervical neoplasia and photodynamic therapy, no filters, and limits were used. After that, all found articles were screened by title and abstract. The last step was a full-text analysis of the selected articles and the reference lists of the articles assessed for eligibility. The last date when the electronic database Cochrane was used is 20.02.2021.

The search using MeSH-terms was also conducted on the electronic database Cochrane library. Firstly, using the advanced search, the following MeSH descriptors were added: "LSIL", "HSIL", "CIN", "PDT", «cervical cancer», no filters and limits were used. Then reviewers screened all the articles in order to find a new one. The last date when the MeSH terms on the Cochrane library were searched is 04.05.2021.

The search strategy in the electronic database Google scholar was similar to the one in Cochrane. The search was conducted using the following combination of the search terms: (photodynamic treatment OR PDT) AND (cervical cancer OR CIN OR LSIL OR HSIL). No filters and limits were used. After that, all found articles were researched by title and abstract. Then full texts of the selected articles were screened. Finally, the reference lists of the pertinent articles were searched for additional potential studies. The last date when the electronic database Google scholar was searched, is 23.02.2021

The search was also conducted in the electronic database ClinicalTrials.gov using advanced search and the following search terms: «Cervical neoplasia» as a condition or disease and «PDT» as an intervention. No filters and limits were used. All found articles were screened by title and protocol of the study. The last date when the electronic database ClinicalTrials.gov was searched is 05.03.2021.

Randomized and non-randomized controlled trials (RCTs) were included in the meta-analysis and the qualitative analysis. Studies

meeting the following inclusion criteria were selected for further analysis: all patients had confirmed LSIL, HSIL, or an early-stage cervical cancer – IA; all patients were treated with PDT with any type of photosensitizer and any type of wavelength. Exclusion criteria of our review were the following: women who were previously treated with PDT; Anamnesis record: porphyria, previously identified cancer of various localization, misbirth, infections; women with cervical cancer 1B or higher. Intervention is photodynamic treatment with any type of photosensitizer using any given wavelength. The comparison is placebo or any other type of treatment.

The primary analysis was aimed to estimate the efficacy of PDT in women with cervical intraepithelial neoplasia and cervical cancer. The outcome was expressed as the cytolytic or/and histological regression in contrast to the placebo group or group of patients with another type of treatment.

Secondary analysis compared the results of PDT in women with cervical intraepithelial neoplasia and cervical cancer to determine the stage with the most successful results of PDT.

Risk of bias assessment was carried out for each included study using the Cochrane Handbook for Systematic Reviews of Interventions. [6-8]

3. Results

The whole search strategy with the results is also presented in flow-diagram (Figure 1) 2213 articles were found after the search was conducted, 34 of which were duplicates and therefore were excluded, 43 of them were review articles and also were excluded because, in our systematic review, we accepted only randomized and non-randomized clinical trials. After that, 2136 articles were analyzed, 2107 of which were excluded by the titles and abstracts. Consequently, 29 publications were left for the full-text screening. All these articles were analyzed following our inclusion and exclusion criteria specified in the protocol registered on PRISMA. Out of these 29 articles, only six were included in our qualitative analyses. Additionally, 143 articles were found in references of the six articles included in the qualitative analyses. Thirty-nine of them met the eligibility criteria. However, none of these studies was included in the systematic review because they were duplicates of the articles that were found earlier.

Among 29 articles, full texts of which were analyzed, [9-37] 6 publications were selected for qualitative analysis. 4 publications [24,28,31, 32] are randomized studies; 2 publications [17,26] are non-randomized studies.

All articles emphasized that PDT is a non-invasive, low-cost procedure that can be performed in women who want to preserve the cervix and avoid premature birth. Three articles noted that CIN 1 has a high probability of spontaneous regression. The photosensitizer was administered intravenously only in one publication. The rest applied it topically. With the intravenous route of administration, PDT proved to be more effective. In two articles, the photosensitizer distribution along the cervical epithelium was studied, which helps to contribute to a more thoughtful treatment.

The publication by Barnett et al. [32] did not prove the effectiveness of PDT in CIN1 and CIN1/2. The study involved 35 people: 12 patients were in the treatment group; 13 patients were in the placebo group. There were no significant differences in outcomes between the treatment group and the control group after 3 months of PDT ($P > 0.9$). 4 patients (31%) had a complete recovery from CIN, five patients (38%) exhibited no changes in grade CIN, that was before treatment, and four patients even showed progression of CIN in the treatment group. On the other hand, the outcomes in the control group were almost the same: 4 patients (33%) showed complete recovery, 5 women (42%) had no changes in the grade of CIN, and patients (25%) exhibited more advanced disease.

Side effects were observed only in the treatment group: some patients experienced vaginal discomfort during illumination, but no pain relief was needed; several women noted watery vaginal discharge and pelvic pain within two weeks after illumination. Patients received ALA 10g 3% applied to the cervix in a contraceptive cap for 4 hours before illumination. The wavelength was 635 nm. Authors note that an increase in the dose of ALA did not increase its accumulation in the cells of the cervical epithelium. By the way, it was not possible to distinguish dysplastic tissues from normal tissues at Pp9 fluorescence.

The authors suggest that the Pp9 concentration was insufficient for effective PDT treatment. Therefore, alternative pathways for the delivery of ALA to the cervical epithelium are required.

The publication by Yu Fu et al. [28] demonstrated fairly high efficacy of PDT in CIN 1. However, it is essential to note that there were not enough patients in the treatment and control groups: 6 women and 5 women, respectively. 5-ALA 10% was used as a photosensitizer, which was locally applied to the cervical epithelium. The PDT procedure was performed 3 times with an interval of 2 weeks. The wavelength was 635 nm. The outcomes were evaluated after 9 months of observation. There were 5 CIN 1 conversion cases (83.33%) in the treatment group, and there were no cases of CIN improvement in the control group ($P < 0.01$). Side effects included local burning and vaginal discharge (did not need treatment). Some doubts about the fairness of the experiment are raised because the control group did not undergo any intervention. The control group received only follow-up. It means that the study was not blind.

The dose-dependent efficacy of PDT in CIN 2 was demonstrated in a publication by Hilleman's et al. [31]. Using an intravaginal device, the treatment was carried out with HAL 5%, 1%, 0.2%. Gynaecologists used an intravaginal device that the patients could remove on their own. It allows to conduct PDT on an outpatient basis and does not disrupt women's daily activities. This device delivers HAL to the cervix in a targeted manner for 5 hours and then automatically produces illumination with wavelength 629 nm for 4.6 hours.

The best response to treatment was noted using HAL 5%. 18/19 patients showed improvement three months after treatment: 4 had normal histology and cytology, and 14 others decreased the CIN grade. None of the patients had normal histology and cytology in the control group, and improvement was noted in 12 of 21 patients (57%) ($P = 0.009$). A stable result was maintained in 18/19 patients (95%) in the treatment group six months after treatment. Improvement was noted in only 13 of 21 patients (62%) in the placebo group. These outcomes demonstrated statistically significant differences between the treatment and control groups ($P = 0.21$).

Some women noted local discomfort, vaginal discharge, and spotting. The authors reported no statistically significant differences between the control and the treatment group among patients with CIN1. They believe that there is a high probability of spontaneous regression of CIN1. Patients with CIN3 were not included in the PDT efficacy analysis because this grade is considered precancerous, so surgery is preferred.

The long-term efficacy of PDT for low-grade and high-grade CIN has been investigated in the publication by Inada et al. [17]. The treatment group consisted of 56 patients with CIN1 and ten patients with CIN2/3. The placebo group consisted of patients who received only radiation and patients who received only cream with MAL. The study's authors considered that it is crucial to have such a distribution to exclude the sole influence of cream or light on treatment results. MAL 20% was used as a photosensitizer, locally applied on the cervix for 1 hour in patients with CIN1 and for 3 hours in patients with CIN2/3. Then fluorescence imaging was performed to control the distribution of Pp9. It was followed by PDT: 21 minutes in patients with CIN1 and 25 minutes in patients with CIN2/3. The wavelength was 630 nm. Patients with low-grade CIN were treated with a single session, and patients with high-grade CIN received treatment twice, with a one-week interval. Visual control was also carried out using a device after PDT to monitor the consumption of Pp9. The observation period was 2 years. As a result, complete regression of CIN1 was demonstrated in 42/56 (75%) patients. In 3/56 women (5.4%), the grade of neoplasia did not change, and in 5/56 patients (8.9%) the progression of CIN1 to CIN2 was noted. 5 patients (8.9%) had a recurrence. One person was lost during the period of

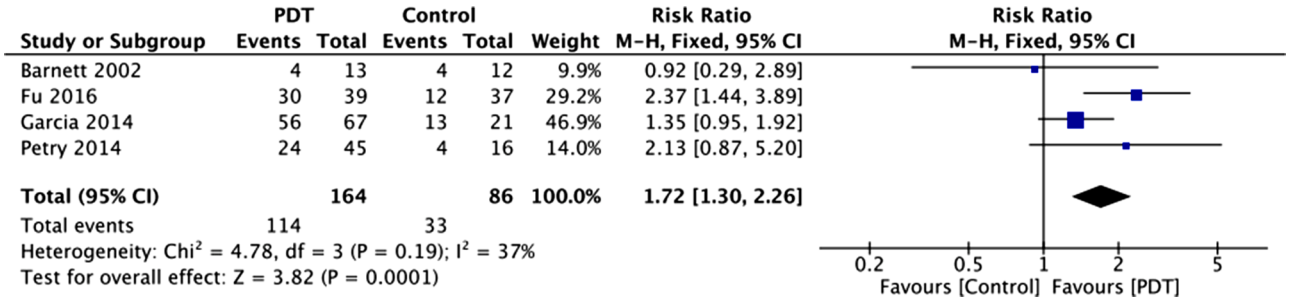

Fig. 2. Meta-analysis of CIN regression after PDT compared with control group.

follow-up.

9/10 (90%) patients with CIN2 exhibited the absence of dysplasia. One woman (10%) had high-grade CIN after 2 years of follow-up. Unfortunately, P-value is not specified in this publication.

The patients reported no side effects.

Min Chui Choi et al. [26] fundamentally differ from other publications included in the qualitative analysis. Firstly, it investigated the efficacy of PDT in patients with high-grade CIN. Secondly, the authors proposed the use of PDT in combination with LEEP or Cone. Thirdly, the photosensitizer was delivered to the body via intravenous injection. Photogem was used as a photosensitizer, which was injected intravenously at a dose of 2 mg/kg 48 hours before the start of laser irradiation with wavelength 630 nm. We want to note that this way of drug administration carries more side effects than a local application of the gel. The photosensitizer makes the eyes and skin sensitive to light. Patients need to wear sunglasses and protect the skin from exposure to light for 6 weeks to avoid systemic side effects. This compulsory measure is inconvenient for patients and increases the length of hospital stay.

A total of 59 patients were enrolled in this study. The patients were divided into 4 groups. We were interested in all of them: Group 1 (13 patients) has received only PDT, Group 2 (15 patients) has received PDT combined with LEEP/Cone, Group 3 (25 patients) has received PDT within 3 months after LEEP/cone due to positive margin, Group 4 (6 patients) has received PDT due to recurrent CIN at least 12 months after LEEP/Cone. To improve treatment outcomes, the authors tried to correct the disadvantages of previous studies. They used a unique fiber that is capable of irradiating the endocervix. They also included high-grade CIN patients in the study so that the probability of self-regression was low.

Thus, the following results were obtained after one year of observation:

In Group 1 - complete remission in 2/2 patients with CIN2, in 6/6 (100%) patients with CIN3, in 4/5 patients (80%) with CIS. 1 patient underwent secondary PDT due to residual lesions and eventually also had CR. CR rate in only PDT group = 100%.

In Group 2 - complete remission in 1/1 patients (100%) with CIN2, in 7/7 patients (100%) with CIN3, in 7/7 patients with CIS. CR rate in PDT + LEEP/Cone group is 100%. Thus, PDT combined with LEEP/Cone may be considered a promising treatment for CIN and cervical cancer in young women who wish to preserve fertility.

In Group 3 – complete remission in 7/7 (100%) patients with CIN3. 2 patients with CIN3 were lost during the study. Complete remission in 15/15 (100%) patients with CIS. 1 patient with CIS was lost during the study. CR rate in PDT within 3 months after LEEP/cone due to positive margin is 100%.

In Group 4 – complete remission in 1/1 (100%) patients with CIN2, in 2/2 (100%) patients with CIN3, in 2/3 (67%) patients with CIS, 1 patient with CIS in this group had residual disease. CR rate in PDT due to recurrent CIN at least 12 months after LEEP/Cone is 83% (5/6). Unfortunately, P-value is not specified in this publication.

There were 70 patients with CIN1 in the prospective, double-blind study by P.Hillemanns et al. [24]. They were divided into three

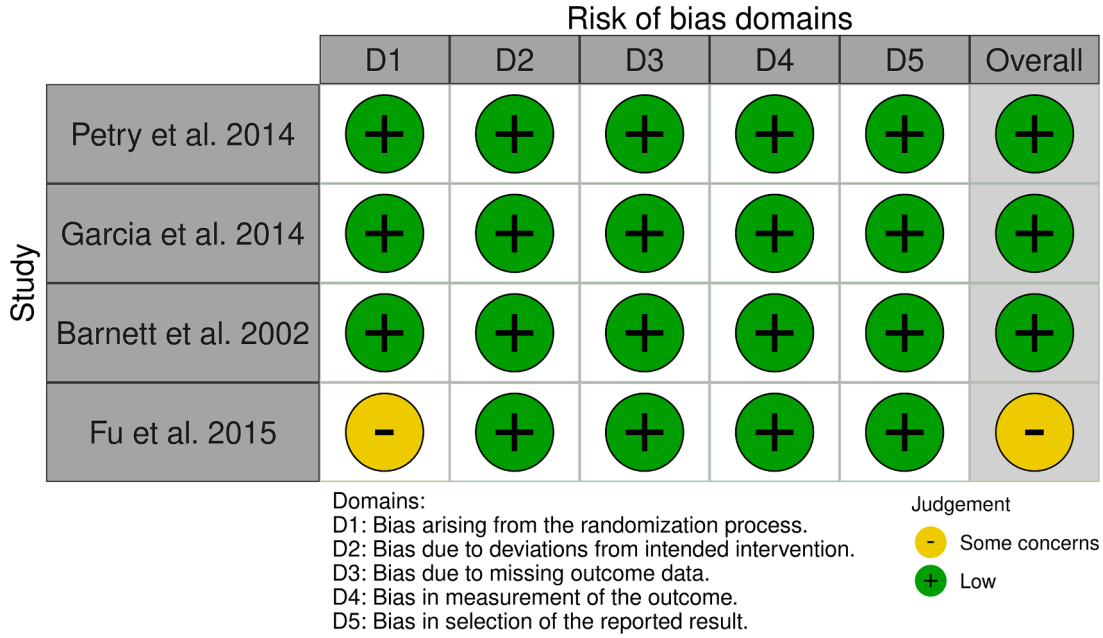

Fig. 3. RoB2.0 tool for randomized controlled trials (Traffic light plot).

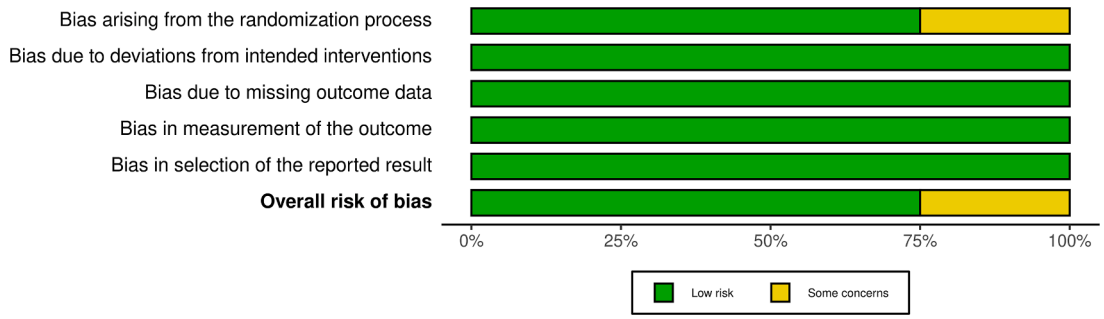

Fig. 4. RoB2.0 tool for randomized controlled trials (Summary plot).

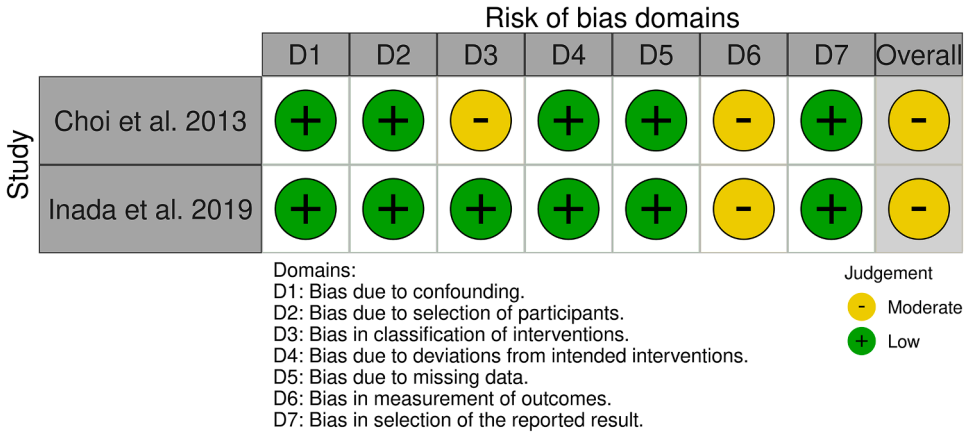

Fig. 5. ROBINS-I tool for non-randomized studies of interventions (Traffic light plot).

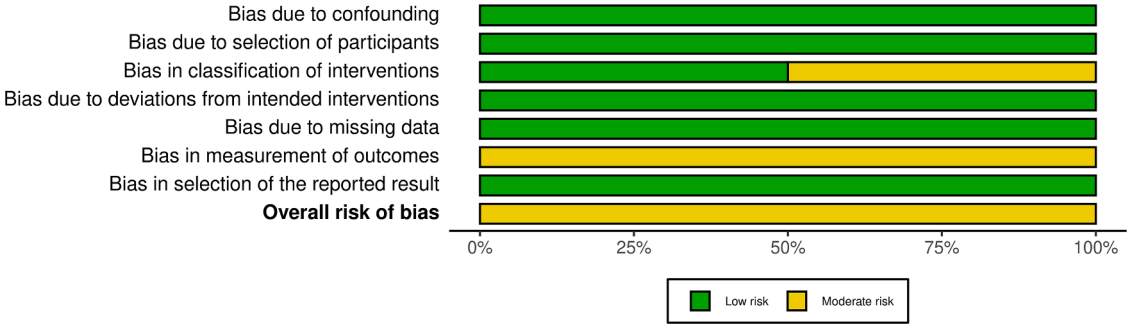

Fig. 6. ROBINS-I tool for non-randomized studies of interventions (Summary plot).

groups: HAL vaginal suppository (47), placebo vaginal suppository (12) or follow-up only (11). HAL is used as a photosensitizer, but concentration was not specified. The wavelength was 633 nm. After 6 months after PDT CIN lesions had cleared in 57% (20/35) of patients in the HAL-PDT group and in 25% (4/16) in the combined control group (P=0.04). Considering that patients noted mild adverse events, the study showed the effectiveness of PDT in CIN1. However, patients noted such side effects as local discomfort, including pain, cramping, and leucorrhea.

The primary analysis was focused on regression of CIN and cancer after PDT. In this meta-analysis, only patients with CIN in 4 studies were included. These 4 clinical trials compared the effectiveness of PDT with control (placebo) groups: (RR = 1.72, 95% CI: 1.30 to 2.26, P = .0001). The heterogeneity for this comparison was 37%. Consequently, PDT showed effectiveness regarding CIN regression (Figure 2).

According to the Cochrane Handbook, four reviewers (J.D., K.M., A. Kh., R.M.) assessed the risk of bias of each included study. In the RoB 2 tool, each item was classified as high, some concerns, or low risk of bias. In addition, each item was classified as critical, serious, or low risk of bias in the ROBINS-I tool. Any disagreements were resolved by discussion with other authors (A.U., L.P.).

Visualization tools were created by the ROBVIS app [38], which made "traffic light" plots of the domain-level judgments for each result and weighted bar plots of the distribution of risk-of-bias judgments within each bias domain (Figures 3-6).

The overall risk of bias for the non-randomized trials was moderate, according to the ROBINS-I tool. The RoB 2 tool indicated mostly low risk regarding overall bias for the randomized trials.

4. Discussion

Cervical intraepithelial neoplasia and cervical cancer, as discussed earlier, still pose a severe problem to the global medical community, as the incidence of these pathologies is increasing each year, especially in

Table 1
Description of articles included in the systematic review.

Author, Year	Study design	N°	PDT application	The wave length, nm	Examination	Follow-up period, months	CRR	PR with stages specifi-cation	Stabili-zation	Progression with stages specification
Peter Hillemanns, 2014	Prospective double-blind study	59	HAL vaginal suppositories 100 mg of hexamino-levulinate hydro-chloride	633	Colposcopy, cytology and HPV	3-6	Treatmentgroup-57,1% (20/35) Controlgroup-25.0% (4/16)			
Min Chul Choi, 2013	Retro-spective study	28	Photogem intravenous 2mg/kg 48 hours before lazer	630	BiopsyHPV DNA	6-120	Group1: PDT only – CIN2: 2/2 (100%), CIN3: 6/6 (100%), CIS: 4/5 (80%) 1 patient with CIS underwent secondary PDT due to residual lesions and received CR finally. CR rate = 100% (13/13) Group2: PDT+cone/leep – dx, CIN2: 1/1 (100%), CIN3: 7/7 (100%), CIS: 7/7 (100%), CR rate = 100% (15/15) Group3: PDT within 3 months after LEEP/cone due to positive margin. CIN3: 7/7(100%), 2 patients with CIN3 were lost. CIS: 15/15 (100%), 1 patient with CIS was lost. CR rate=100% (22/22), 3 patients in this group were lost. Group4: PDT due to recurrent CIN at least 12 months after LEEP/Cone. CIN2: 1/1 (100%). CIN3: 2/2 (100%). CIS: 2/3 (67%), 1 patient with CIS had residual disease. CR rate= 83% (5/6).			
Natalia Mayumi Inada, 2019	Retro-spective	76	1 h of MAL application and 100.8 J/cm2 of fluency	630		24	Beforetreatment: CIN1 group-56 CIN2/3-10 PLACEBO- 10 patients PLACEBO: CRR 6/10 Treatmentgroup: 35/56 patients with CIN1 had CRR(62,5%). 2/10 patients with CIN2/3 had CRR(20%)	CIN2/3 group: partial regression to CIN1 - 2/10	CIN1 group 8/56 (14,3%) CIN2/3 group: 6/10 PLA-CEBO group 1/10	CIN1 group 5 (8,9%)
Adrian A. Barnett, 2002	Randomized, double-blind, placebo-controlled	25	10 g of 3% ALA in Intrasite Gel applied to the cervix in a contraceptive cervical cap	635	PAP-test, colposcopy, biopsy	3	Treatmentgroupbeforetreatment: CIN1-10 CIN1/2-2 Aftertreatment: CRR -4 (33%) Placebogroupbeforetreatment: CIN1-12 CIN1/2-1 Aftertreatment: CRR-4 (31%)		Placebo group: 5-38% Treatment group: 5-42%	Placebo group: 4-31% Treat-ment group: 3-25%
Peter Hillemanns, 2014	Double-blind randomized placebo-controlled	262	topical treatments of HAL hydrochloride 0.2%, 1%, 5%	629	Colposcopy, biopsy	3-6	3months HAL5% CRR in CIN2-95% (18/19) PLACEBO- 57% (12/21) 6months CRR in CIN2- 95% (18/19) PLACEBO -62% (13/21)			
Yu Fu, 2015	Prospective study	11	10% ALA thermogel applied on cervix	635	Colposcopic biopsy, HPV DNA histopatho-logy	3-9	9 month follow-up 83,3% (5/6) -treatment group 0% (0/5)- control group			

young women. In case of ineffectiveness of various existing methods of treatment offered by the clinical guidelines (laser surgery, diathermocoagulation, cryotherapy, large loop excision of the transformation zone (LEEP/LLETZ), cold knife conization (CKC), radio- and chemotherapy), hysterectomy is considered, which is unacceptable for young patients willing to conceive later in the course of their life. Thus, clinicians worldwide are searching for other treatment methods that are believed to increase regression rates if combined with other treatment options or applied as monotherapy. Table 1

Photodynamic therapy is a non-invasive method that uses a drug designed to destroy cancerous and dysplastic cells following photoactivation by the light of a specific wavelength. Its application in gynaecology is very promising since it is considered a conservative method of therapy that spares women's reproductive potential, allows outpatient care, causes minimal side effects that do not require immediate correction, and does not interfere with the women's routine. In a systematic review of clinical trials, we have found that photodynamic therapy as a treatment option for LSIL, HSIL, and cervical cancer proves to be effective compared to placebo. Although this method has many advantages, it is still not routinely used in clinical practice and is not approved by the medical community due to the controversy existing around its effectiveness.

We have found many studies that demonstrated positive results of PDT in LSIL, HSIL, and CIS while looking for publications for our systematic review. Unfortunately, the design of these studies did not follow our review protocol (they did not have control groups), and we were unable to include them. Efficacy of PDT in CIN and cervical cancer was shown with intravenous administration of a photosensitizer. Excellent results were obtained in Istomin's publication [25]: complete regression was in 23/24 (95.83%) patients with CIN2 and in 81/88 (92.05%) patients with CIN3. According to Ishimura's results [20], complete remission (CR) was in 31 patients (100%) (2 patients with CIN2 and 29 patients with CIN3) a year after PDT treatment. 90% (94/105) of patients with CIN1, CIN2, CIN3 in Yamaguchi's study [29] had CR after 3 months. In the publication by Ye-Kyu [37], in which intravenous administration of a photosensitizer was used, promising results were also demonstrated: 18/19 (95%) patients with CIN2, CIN3, and 2/3 with CIS (67%) patients exhibited CR. In Trushina's publication [22], PDT was investigated in HSIL and CIS. 50/56 (89.2%) patients with CIN3 and 11/16 (68.8%) patients with CIS had CR.

Despite the favorable outcomes of our review, several limitations can impact these results. Firstly, during the selection process, it was noted that some studies prefer intravenous administration of photosensitizer rather than its topical application. Indeed, such a route of administration is followed by promising results shown by the complete elimination of cancerous or precancerous cells and perseverance of normal epithelium during an extended period. Istomin et al.[25] chose Chlorin e6-PVP (PhotolonTM) intravenously 1-2,5 mg/kg 30 min as a photosensitizing agent in their clinical trial and reported that 96% (23 out of 24) of patients with CIN II and 92% (81 out of 88) with CIN III showed no signs of dysplasia after treatment. However, according to the authors, this procedure has its own consequences, which lead to special restrictions. For instance, patients needed to maintain a restricted light regimen during the first days after intravenous PDT. Secondly, articles included in the review differ by the duration of the follow-up period within which patients were evaluated for any signs of abnormal cervical epithelium: Barnett et al. [32] conducted follow-up examinations throughout 3 months, while Inada et al. [17] – 24 months. There is insufficient evidence proving whether prolongation or shortening of the follow-up period can substantially change the results, but it is supposed that tissue alterations in the cervix may occur even after the end of a given follow-up period. Thirdly, several studies [26] find it essential to eliminate dysplasia in the cervix so that some patients with no improvement after first PDT undergo repeated PDT until no signs of HSIL and LSIL were seen in patients. Such a tactic may contribute to the heterogeneity of patients included in the review. Also, it was interesting to note that in Barnett et al. study local anesthesia was administered before the application of the photosensitizer, which could affect the result of the control group, due to the malabsorption. [32] Unfortunately, there was no evidence that could confirm this theory. Nevertheless, we assume that local anesthesia had an influence on the study results. Finally, among clinical trials included in our review, there are studies with an unequal number of patients in control and treatment groups (usually, the control group included fewer patients than the treatment group). We think that groups should be homogeneous and unbiased to yield reliable results. On the other hand, some of these studies [17] comment that such distribution of patients is statistically insignificant and does not affect the results.

Implications for future research may include more randomized clinical trials that can investigate PDT and its effectiveness with or without local anaesthesia and intravenous injection of photosensitizer and its safety. Moreover, we need more well-conducted studies with appropriate study designs and a significant amount of patients to obtain more in-depth information regarding PDT in patients with cervical pathology.

5. Conclusion

Based on our systematic review and meta-analysis, it could be concluded that photodynamic therapy may be an effective approach in CIN (LSIL) regression compared with placebo. Nevertheless, we need more evidence and long-term follow-up to answer all questions completely.

Other

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